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ORIGINAL ARTICLE



HNF1B nephropathy has a slow-progressive phenotype in childhood—with the exception of very early onset cases: results of the German Multicenter *HNF1B* Childhood Registry

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Abstract

Background *HNF1B* gene mutations are an important cause of bilateral (cystic) dysplasia in children, complicated by chronic renal insufficiency. The clinical variability, the absence of genotype-phenotype correlations, and limited long-term data render counseling of affected families difficult.

Methods Longitudinal data of 62 children probands with genetically proven *HNF1B* nephropathy was obtained in a multicenter approach. Genetic family cascade screening was performed in 30/62 cases.

Results Eighty-seven percent of patients had bilateral dysplasia, 74% visible bilateral, and 16% unilateral renal cysts at the end of observation. Cyst development was non-progressive in 72% with a mean glomerular filtration rate (GFR) loss of $-0.33 \text{ ml/min/1.73m}^2$ per year (± 8.9). In patients with an increase in cyst number, the annual GFR reduction was $-2.8 \text{ ml/min/1.73m}^2$ (± 13.2), in the total cohort $-1.0 \text{ ml/min/1.73m}^2$ (± 10.3). A subset of *HNF1B* patients differs from this group and develops end stage renal disease (ESRD) at very early ages < 2 years. Hyperuricemia (37%) was a frequent finding at young age (median 1 year), whereas hypomagnesemia (24%), elevated liver enzymes (21%), and hyperglycemia (8%) showed an increased incidence in the teenager

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child. Genetic analysis revealed no genotype-phenotype correlations but a significant parent-of-origin effect with a preponderance of 81% of maternal inheritance in dominant cases.

Conclusions In most children, *HNFI1B* nephropathy has a non-progressive course of cyst development and a slow-progressive course of kidney function. A subgroup of patients developed ESRD at very young age < 2 years requiring special medical attention. The parent-of-origin effect suggests an influence of epigenetic modifiers in *HNFI1B* disease.

Keywords Cystic kidney disease · *HNFI1B* · Hypomagnesemia · GFR decline · MODY

Introduction

Congenital anomalies of the kidneys including renal dysplasia are a common cause of renal failure in children [1]. Diagnosis of kidney dysplasia in clinical routine is based on ultrasonography, showing an echo-bright kidney with or without cysts and poor corticomedullary differentiation [2]. Renal histology defines kidney dysplasia by showing incompletely branched ducts surrounded by undifferentiated and metaplastic stroma [3, 4]. In a significant number of cases, gene mutations in *HNFI1B* on chromosome 17q21.3 have been identified as underlying cause. *HNFI1B* encodes for hepatocyte nuclear factor-1 β (HNF-1 β), a transcription factor that is expressed early in embryonic development. HNF-1 β acts as a homo- or heterodimer with HNF-1 α and plays a key role for tissue-specific regulations of gene expression in various organs such as the kidneys, liver, biliary ducts, pancreas, and the urogenital tract [5, 6]. First, *HNFI1B* gene mutations were identified in patients with maturity onset diabetes of the young (MODY 5) in 1997 [7]. Today, *HNFI1B* disease is recognized to represent an autosomal dominant syndromal disorder comprising renal cystic disease, diabetes mellitus, elevated liver enzymes, hyperuricemia, and pancreatic and genital tract malformations (MIM 137920; renal cysts and diabetes syndrome, RCAD) [8]. Some patients with *HNFI1B* mutations show hypomagnesemia caused by hypermagnesiuria [9] which is in part due to the control of *FXYD2* expression by HNF-1 β in the distal tubule [10]. *HNFI1B* mutations are also identified in pediatric patients with isolated renal dysplasia with cysts [11–14]. The nephropathy in these cases is part of the autosomal dominant tubulointerstitial kidney disease spectrum ADTKD [15], formerly known as medullary cystic kidney disease (MCKD). Next to *HNFI1B* three other genes (*MUC1*, *UMOD*, and *REN*) with shared clinical features have been assigned to this prototypic group of nephropathies. We here focussed on genetically proven *HNFI1B* nephropathy in children and sought to define the longitudinal clinical course, the progression of renal disease, and the manifestation of extrarenal symptoms. For this purpose, we initiated a national clinical registry encompassing a pediatric cohort of young age. Additional data from the Czech Republic and Poland were included in a collaborative approach.

Material and methods

Patients

Sixty-two children probands (39 males; aged 0–18 years) treated at one of 11 pediatric nephrology units in Germany, the Czech Republic, and Poland, were recruited, and annual data were collected from a total of 323 questionnaires (median follow-up 4 years; range 1 month–19 years, Suppl. Material 1a, b). Clinical and laboratory data as well as repeated renal ultrasound data were collected as described below. All patients entered in the study had primarily been seen by expert pediatric nephrologists. A renal phenotype with cystic or non-cystic kidney dysplasia and/or tubulointerstitial kidney disease (TKD) led to the initiation of *HNFI1B* mutational analysis. Inclusion criterion of the study was confirmed *HNFI1B* nephropathy with proven mutation in *HNFI1B*. For this reason, the *HNFI1B* score published by Faguer et al. [16] to identify patients suitable for *HNFI1B* mutation testing was not applicable in the present study.

Mutation analysis

Genomic deoxyribonucleic acid (DNA) was extracted from peripheral blood. Exons 1–9 of *HNFI1B*, including intron-exon boundaries, were amplified by polymerase chain reaction (PCR) and subjected to exon-specific next-generation sequencing (NGS) and Sanger sequencing. The result was compared to the published sequence NM_000458.2. Multiplex ligation-dependent probe amplification (MLPA) analysis was performed to determine the presence of copy number variations, deletions, or duplications (SALSA MLPA P241 probe mix; MRC-Holland, Amsterdam, Netherlands) [17], including *GCK*, *HNFI1A*, *HNFI1B*, and *HNFI4A*.

Renal ultrasound

Repeated renal ultrasound examinations were performed annually at each center. Renal dysplasia was defined as poor corticomedullary differentiation, echo-bright kidneys, or both [2]. For medical and ethical reasons, affected children are generally not biopsied which might be a limitation of the study. Renal cysts were categorized by number ($n \leq 5$ or $n > 5$), and a cyst score was applied to define an increase in cyst

number over time (no cysts, score 0; ≤ 5 cysts, score 1; > 5 cysts, score 2). Progressive disease was defined as cyst progression in at least one kidney.

Clinical and laboratory data

Baseline and follow-up data of age, height, onset of nephropathy, ESRD, hypomagnesemia, hyperglycemia, hyperuricemia, elevated liver enzyme activity, exocrine pancreas insufficiency, and anomalies of the genital tract were documented following external physical and ultrasound examination and laboratory assessment. Age-dependent reference limits were applied [18–20]. Hypomagnesemia was defined as repeated serum magnesium concentrations lower than 0.65 mmol/l. The estimated glomerular filtration rate (eGFR) was calculated from serum creatinine and body height according to the Schwartz formula [21]. The CKD Work Group's KDIGO guidelines were used to define chronic kidney disease (CKD) stages I–V [22].

Family histories were documented including genetic results and reported *HNF1B*-related symptoms as provided by the cooperating centers.

Statistical analysis

Data are given as the median and/or mean with standard deviation (SD). Statistical analysis was assessed using Student's *t* test. Statistical significance was defined as $p \leq 0.05$.

Results

Genetics

HNF1B whole gene deletions (exons 1–9) were detected in 33/62 patients (53%), missense mutations in 11 (18%), nonsense (stop) mutations in 7 (11%), and splice mutations/gross insertions in 11 (18%) (Table 1). Parental DNA of 28 families (30 patients) was subjected to cascade screening, and parental transmission of *HNF1B* gene mutations was observed in 16/28 families with maternal transmission in 13/16 (81%) and paternal in 3/16 (19%). 11/16 (71%) parental mutation carriers exhibited symptoms related to *HNF1B*. Four parental mutation carriers had no documented clinical symptoms. We have no information whether a systematic screening in these four individuals was performed which is a limitation of this study. In one parental mutation carrier with proven genetic result, no clinical information was available. De novo mutations were detected in 12/30 patients (40%). Among these, 10/12 (83%) constitute complete gene deletions, 1/12 a missense, and 1/12 a stop mutation. Three missense mutations (Asp82Asn, Val61Gly, and Gly76Cys) are annotated in the gnomAD database with allele frequencies of approximately 1–2:1000 in

large populations of different ethnic origins (<http://gnomad.broadinstitute.org>); however, the phenotype of the study patient affected by Asp82Asn shows typical *HNF1B* disease, and both Val61Gly and Gly76Cys have been reported in different *HNF1B* studies in patients with *HNF1B* disease (<http://www.hgmd.cf.ac.uk>). As CAKUT is as frequent as 1% in the general population, these missense mutations most likely represent hypomorphic variants associated with *HNF1B* disease in conjunction with other genetic or environmental events [12, 23]. The same holds true for patient 10, offspring of consanguineous union and affected by a homozygous Arg232Cys mutation, and a full-blown picture of *HNF1B* disease.

There were no statistically significant differences in renal function or phenotypes among carriers of different *HNF1B* mutation types ($p > 0.05$ between all groups; Table 2 and Suppl. Table 1). The mean GFR at the end of observation in the group of patients with deletions was 106.8 ml/min/1.73m² (mean age 12.0 years, median age 8.0 years) vs. 98.0 ml/min/1.73m² (mean age 8.4 years, median age 7.0 years) in the group with non-deletion mutations ($p > 0.05$).

Renal phenotype

Prenatal dysplasia was documented for 32/62 patients (52%); (no data $n = 30$). At the end of follow-up, ultrasound revealed bilateral dysplasia in 54 patients (87%), unilateral dysplasia in 3, unilateral dysplasia with contralateral agenesis in 4, and no documented dysplasia in 1 (Fig. 1a).

Bilateral renal cysts—at the end of follow-up—were present in 46/62 patients (74%), unilateral cysts in 10 (16%), and no cysts in 6 (10%). Most patients experienced no statistically significant increase ($p > 0.05$) in the number of renal cysts at a median follow-up of 4 years (mean 5.2 years; range 1 month–19 years). Of the total cohort with at least two renal ultrasound examinations, no increase was documented in 34/47 patients (72%); and an increase in 13/47 patients (28%): in 4 patients, cysts were observed for the first time during the course of the study; and in nine patients, the cyst score increased from 1 to 2; Fig. 1b).

At the end of follow-up, bilateral dysplasia with cysts was found in 46/62 patients (74%), and unilateral dysplasia with cysts and contralateral kidney agenesis was found in two. Unilateral cystic dysplasia with a normal contralateral kidney was documented for eight patients (13%). From the remaining six patients, five showed renal dysplasia but no cysts.

Renal function

Kidney function exhibited wide interindividual variability. At the end of follow-up, ESRD was documented in 5/62 (8%) with a median age of 15 months (range 3 months–6 years); all

Table 1 Patient cohort

Patient	Gender	<i>HNF1B</i> mutation	Classification	Renal sonography	Extrarenal manifestations	CKD	Family genetics	Family history
1	m	c.244G > A; p.Asp82Asn (het) [§]	Missense	D, C	U	1	ND	
2	m	c.182 T > G; p.Val61Gly (het) [§]	Missense	D, c		1	ND	
3	m	DEL (het)	Deletion	D,	L	1	ND	
4	m	DEL (het)	Deletion	D, c	U	5	ND	
5	f	c.182 T > G; p.Val61Gly (het) [§]	Missense	D, C		5	ND	
6	m	DEL (het)	Deletion	D, C	L	1	ND	
7	m	c.526C > T; p.Gln176* (het)	Stop	D, C		2	Paternal	No anomalies
8	f	DEL (het)	Deletion	D, C	U, L	2	Maternal	CRI; renal cysts
9	m	c.544 + 3_544 + 6delAAGT (het)	Splice	D, C	U, L	5	Maternal	CRI; renal cysts; uterus bicornis; gestational diabetes
10	m	c.694C > T; p.Arg232Cys (hom) ^{§§}	Missense	d*, c	U, L, M	1	ND	
11	m	DEL (het)	Deletion	D, C		2	Maternal	GFR normal; renal cysts
12	m	c.226G > T; p.Gly76Cys (het) [§]	Missense	D, C	U, L	1	ND	
13	m	DEL (het)	Deletion	D, C		2	ND	
14	f	c.182 T > G; p.Val61Gly (het) [§]	Missense	d, c		2	ND	
15	m	Duplication exon 5 (het)	Gross insertion	D, C		2	Paternal	No anomalies
16	f	Duplication exon 5 (het)	Gross insertion	D, C		1	Paternal	No anomalies
17	f	c.544C > T; p.Gln182* (het)	Stop	D, C		1	Maternal	CRI; unilateral kidney agenesis
18	f	c.544 + 1G > A (het)	Splice	D, C		5	Paternal	CRI
19	f	DEL (het)	Deletion	D, C		1	ND	
20	f	c.544 + 3_544 + 6delAAGT (het)	Splice	D, C	U, M	2	ND	
21	m	DEL (het)	Deletion	D, C	M	3	De novo	
22	m	c.512G > A; p.Trp171* (het)	Stop	D, C		2	Maternal	DM
23	f	c.512G > A; p.Trp171* (het)	Stop	D, C	M	1	Maternal	DM
24	m	c.1339 + 3_6del (het)	Splice	D, C		1	ND	
25	m	DEL (het)	Deletion	TKD ^{§§§}	H, M	1	ND	
26	m	DEL (het)	Deletion	D, C		1	ND	
27	f	DEL (het)	Deletion	D, C	H, U, M	1	ND	
28	m	DEL (het)	Deletion	D, C		1	No data	
29	m	c.554C > T; Gln182* (het)	Stop	D	U, M	2	Maternal	CRI
30	f	c.826C > T; p.Arg276* (het)	Stop	D, C		1	Maternal	Cystic kidney dysplasia
31	f	c.406C > G; p.Gln136Glu (het)	Missense	D, C		5	ND	
32	f	DEL (het)	Deletion	D, c		4	ND	
33	f	DEL (het)	Deletion	D, C	U, L, M	2	ND	
34	m	c.443C > T; p.Ser148Leu (het)	Missense	D, C	U, G, L	4	ND	
35	f	DEL (het)	Deletion	D, C	M	1	De novo	
36	m	DEL (het)	Deletion	D, C		1	ND	
37	m	DEL (het)	Deletion	D, C		3	De novo	
38	m	DEL (het)	Deletion	D, C		1	De novo	
39	m	c.1045 + 12 T > C (het)	Splice	D		2	Maternal	No anomalies
40	m	c.713G > T; p.Trp238Leu (het)	Missense	D, C	L	1	ND	
41	f	DEL (het)	Deletion	D, C		1	ND	
42	m	DEL (het)	Deletion	D, C		1	ND	
43	m	DEL (het)	Deletion	D, C		1	ND	

Table 1 (continued)

Patient	Gender	<i>HNF1B</i> mutation	Classification	Renal sonography	Extrarenal manifestations	CKD	Family genetics	Family history
44	m	DEL (het)	Deletion	D, C	L	1	De novo	
45	f	c.412 G > A; p.Glu138Lys (het)	Missense	D, C		2	De novo	
46	f	DEL (het)	Deletion	D, C	H, U	1	Maternal	Gestational diabetes
47	m	DEL (het)	Deletion	d*		4	ND	
48	f	c.1492C > T; p.Gln498* (het)	Stop	D, C	U	1	De novo	
49	m	DEL (het)	Deletion	D, C		1	ND	
50	m	c.544 + 1 G > T (het)	Splice	D		2	ND	
51	m	DEL (het)	Deletion	D, C		1	De novo	
52	f	DEL (het)	Deletion	D, c		2	ND	
53	m	DEL (het)	Deletion	d*	U, L, M	2	ND	
54	f	c.544 + 3_544 + 6delAAGT (het)	Splice	D, C	H, U	1	ND	
55	m	c.781A > G; p.Arg261Gly (het)	Missense	D, C	U	4	Maternal	MODY 5
56	f	DEL (het)	Deletion	D, c	U	1	De novo	
57	f	c.1340-1G > A	Splice	D, C	U, M	1	Maternal	ND
58	m	DEL (het)	Deletion	D, C	U	1	De novo	
59	m	DEL (het)	Deletion	d*, c		1	De novo	
60	m	c.1340-1G > A	Splice	c		1	Maternal	No anomalies
61	m	DEL (het)	Deletion	D, C		1	De novo	
62	m	DEL (het)	Deletion	D, c	L, M	1	Maternal	Kidney dysplasia; MODY 5

m male; *f*, female; *C* bilateral cysts; *c* unilateral cysts; *D* bilateral dysplasia; *d* unilateral dysplasia; *d** unilateral dysplasia + contralateral agenesis; *G* genital tract anomalies; *H* hyperglycemia; *U* hyperuricemia; *L* elevated liver enzyme activity; *M* hypomagnesemia; *ND* no data. Renal sonography, extrarenal manifestations, and CKD stage documented at last follow-up. [§] Variants are annotated in gnomAD and are considered hypomorphic variants in the context of *HNF1B* disease. ^{§§} Patient is of consanguineous union. ^{§§§} Patient is affected by a phenotype of tubulointerstitial kidney disease (TKD)

had undergone transplantation. The median time from initial diagnosis to ESRD was 7 months (range 1 month–4 years).

At the end of follow-up, CKD I was documented in 36/62 patients (58%), CKD II in 15 (24%), CKD III in 2 (3%), CKD IV in 4 (7%), and CKD V in 5 patients (8%); the median age of study patients was 8 years (range 0–19 years; Fig. 2a).

To calculate the annual reduction in GFR loss, we only included data from patients > 2 years of age—to avoid misinterpretation of early creatinine values—with at least two documented GFR-values. In the total cohort, the mean annual reduction in GFR was $-1.0 \text{ ml/min/1.73 m}^2$ (± 10.3). For the group of patients with an increase in the number of cysts,

the mean annual reduction in GFR was $-2.8 \text{ ml/min/1.73 m}^2$ /year (± 13.2) whereas for the group with no increase in cyst number, the annual GFR development was $-0.33 \text{ ml/min/1.73 m}^2$ (± 9.5).

At study onset, we documented for these patients CKD I in 61% (20/33), CKD II in 27% (9/33), CKD III in 3% (1/33), CKD IV in 9% (3/33), and CKD V in no patient (median age 4 years, range 2–18 years; Fig. 2b).

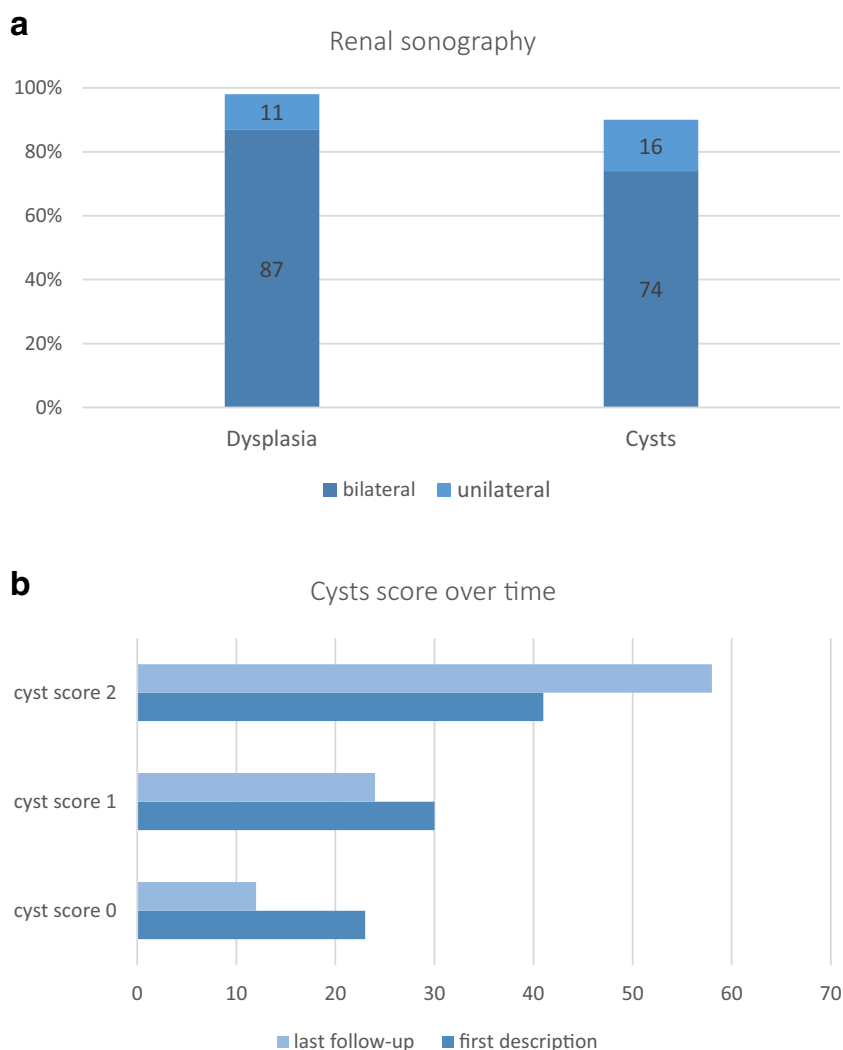
At the end of follow-up in these 33 patients, we documented: CKD I in 64% (21/33), CKD II in 24% (8/33), CKD III in no patient, CKD IV in 9% (3/33), and CKD V in 3% (1/33) (median age 12 years, range 5–19 years; Fig. 2c).

Table 2 Renal function and incidence of extrarenal manifestations, depending on the type of *HNF1B* mutation

Mutation	CKD 1	CKD 2	CKD 3	CKD 4	ESRD	Extrarenal manifestations
Deletion (<i>n</i> = 33)	64% (21/33)	21% (7/33)	6% (2/33)	6% (2/33)	3% (1/33)	42% (14/33)
Missense (<i>n</i> = 11)	46% (5/11)	18% (2/11)	0%	18% (2/11)	18% (2/11)	46% (5/11)
Splice/gross insertion (<i>n</i> = 11)	46% (5/11)	36% (4/11)	0%	0%	18% (2/11)	36% (4/11)
Stop (<i>n</i> = 7)	57% (4/7)	43% (3/7)	0%	0%	0%	43% (3/7)

p value > 0.05 between all groups with respect to the type of mutation

Fig. 1 **a** Prevalence of dysplasia and cysts in patients with *HNF1B* mutation at last follow-up. **b** Cyst score over time ($n = 94$ kidneys from 47 patients with at least two renal ultrasound examinations). In total, 23/94 (24%) kidneys showed a progress. Patients defined as progressive with respect to renal cysts showed a progress in at least one or both kidneys. No progress $n = 34/47$ patients (72%); progress $n = 13/47$ patients (28%). We defined a progress in renal cysts, when there was a progress in at least one of the patients' kidneys



Biochemical data

Hypomagnesemia (Table 3) was detected in 12/50 children (24%) at a median age of 10 years (mean 8.9 years; range 0–16 years). Magnesium values ranged from 0.5 to 0.6 mmol/l (mean 0.55 mmol/l). 7/29 (24%) patients with CKD I presented with hypomagnesemia (median age 12; mean 10; range 0–16 years). In 6/7 patients, hypomagnesemia was diagnosed at the same time as *HNF1B* nephropathy, in one patient 8 years after the initial diagnosis.

Hyperuricemia was detected in 19/52 patients (37%) at a median age of 1 year (range 0–17 years) and already in 11/32 patients (34%) with CKD I. For all patients, hyperuricemia was diagnosed at the same time as *HNF1B* nephropathy. Uric acid concentrations ranged from 363 to 500 $\mu\text{mol/l}$ (mean 429 $\mu\text{mol/l}$). No clinical symptoms of gout were present.

Elevated liver enzyme activity was diagnosed in 12/58 patients (21%) at a median age of 11 years (mean 10.4; range 0–18 years). For eight of these patients, elevated liver enzymes were documented at the same time as *HNF1B* nephropathy at

a median age of 14 years, for four patients with a median lag time of 10.5 years after initial manifestation of *HNF1B* nephropathy.

4/50 patients (8%) experienced recurrent hyperglycemia, elevated HbA1c levels, or both. The age at manifestation was 4, 12, and 14 years, respectively, and in one patient, a neonatal diabetes mellitus (DM) with inhomogeneous pancreas texture was diagnosed shortly after birth.

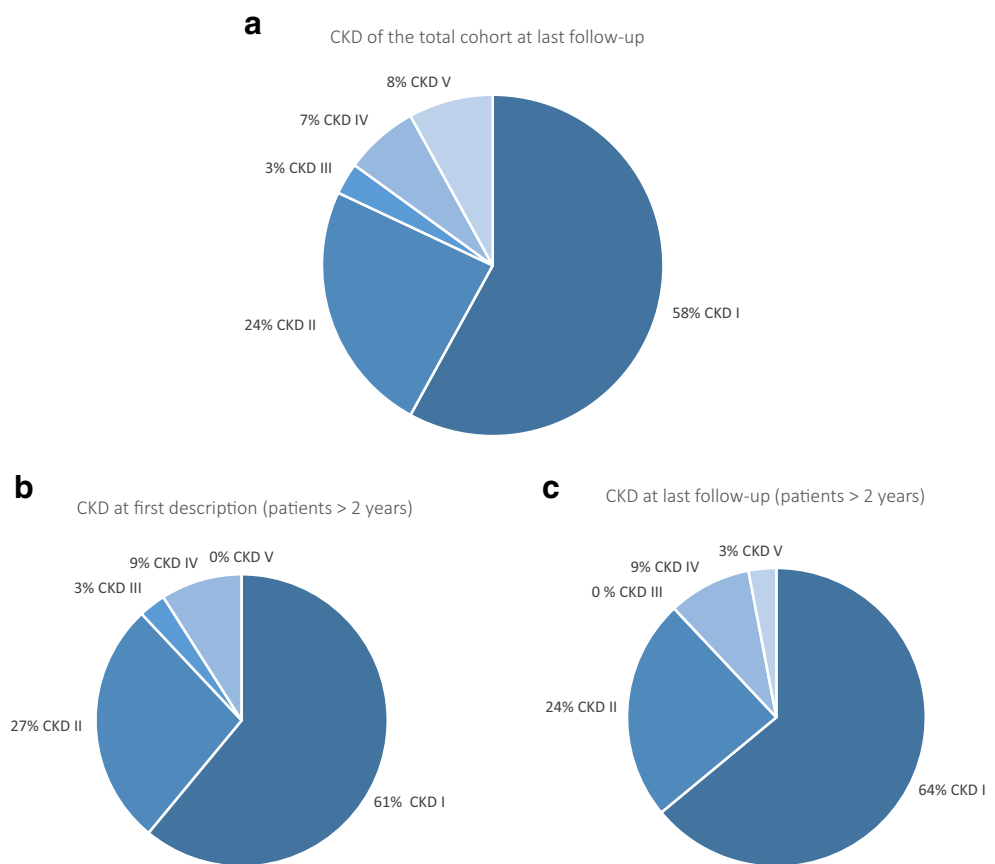
Urogenital abnormalities

One of the 62 patients had hypoplastic testicles; no other urogenital abnormalities were documented.

Discussion

The clinical differential diagnosis of *HNF1B* nephropathy includes other genetic forms of congenital anomalies of the kidneys and urinary tract (CAKUT), ADTKD-*UMOD*, -*MUC1*,

Fig. 2 **a** Chronic kidney disease (CKD) of the total cohort at the end of the observation ($n = 62$, mean 8.2 years, median 8 years, range 0–19 years). **b** Chronic kidney disease (CKD) at first description. Included patients > 2 years to avoid misinterpretation of early creatinine values with at least two follow-ups ($n = 33$, mean 6.3 years, median 4 years, range 2–18 years). **c** Chronic kidney disease (CKD) at last description. Included patients > 2 years to avoid misinterpretation of early creatinine values with at least two follow-ups ($n = 33$, mean 11.2 years, median 12 years, range 7–18 years)



or -REN but also autosomal dominant polycystic kidney disease (ADPKD), depending on the ultrasound picture and extrarenal symptoms. In exceptional cases, ADPKD can manifest itself in very young patients (very early onset [VEO]-ADPKD) [24]. In most adult cases, the prognosis of ADPKD is unfavorable, with consistent growth of cysts and deterioration of renal function. The progression of cyst growth and renal insufficiency in *HNF1B* nephropathy has not been as thoroughly studied so far and was central focus of the here presented study.

Genotype-phenotype correlation

The present work shows a lack of genotype-phenotype correlations among the various types of *HNF1B* gene mutations, as

Table 3 Extrarenal manifestations at the end of observation (median age of the total cohort 8 years, mean 8.2 years)

Extrarenal manifestation	Patients	%	Age at diagnosis
Hypomagnesemia (<0.65 mmol/l)	12/50	24	10.0 years (median)
Hyperuricemia	19/52	37	1.0 year (median)
Elevated liver enzymes	12/58	21	11.0 years (median)
Hyperglycemia	4/50	8	0, 4, 12, 14 years
Urogenital anomalies	1/62	2	Postnatal

has been reported previously [11, 14]. One could have expected gene deletions and loss-of-function mutations with higher frequency in patients with more severe disease as has been reported for other kidney disorders [25, 26]. However, this issue is controversially discussed, and other authors even describe a more favorable renal outcome in patients with gene deletions compared to other mutations in *HNF1B* [27–29]. Possible explanations include a dominant negative effect of *HNF1B* non-deletion mutations or the involvement of other genes located in the deletion interval on chromosome 17q12.3. This interval spans additional 14 genes to *HNF1B* and affected patients are also at risk to develop neuropsychological symptoms. These comprise intellectual disabilities, learning difficulties, externalization disorders as attention-deficit hyperactivity disorder and autistic traits with variable severity [30–32]. Few patients with intellectual disability and intragenic *HNF1B* mutations have also been described [32]. To date, however, no studies have systematically called for expert neuropsychological testing in *HNF1B* patients, such as those included in the present study. Follow-up studies will have to address this important issue strongly impacting the quality of life of affected individuals.

Like in previous studies, *HNF1B* mutations were equally distributed among boys and girls. De novo mutations were observed in 40% of patients with a preponderance of deletion mutations (83%). A similar observation was made in [14].

Paired segmental duplications along with breakpoints are most likely involved in the pathogenesis of this recurrent chromosomal microdeletion [33]. One striking observation of the present study is the high degree (81%) to which *HNF1B* mutations are inherited through the maternal lineage in familial cases. Ulinski et al. reported dominant inheritance in 8/17 families; however, no parental data were presented [11]. In a study involving 42 patients with complete gene deletions, Heidet et al. identified de novo mutations in 14 of these patients; for seven patients, there was proven dominant inheritance, with maternal transmission in 6/7 (86%) [14]. A similar parent-of-origin effect was recently described for non-renal autosomal disease, e.g., familial early puberty [34] and hereditary paraganglioma [35]. Alterations of genomic imprinting or maternal imprinting of modifying genes were believed to be involved in these cases. No cascade testing after routine scans in pregnant women has been performed in our study ruling out a selection bias. Alternatively, the fertility of adult men with *HNF1B* mutations may be reduced. In-depth genetic studies will be necessary to elucidate these parent-of-origin mechanisms.

Renal phenotype

Ninety-eight percent of the study patients showed renal dysplasia and 90% renal cysts. At a median follow-up of 4 years, there was no significant increase in the number of renal cysts in 72% of patients. The mean annual decrease in GFR was $-1.0 \text{ ml/min/1.73m}^2$. These findings indicate that *HNF1B* nephropathy in children is a rather slow-progressive disorder with respect to cyst development and to loss of kidney function. These characteristics distinguish the *HNF1B* phenotype from the polycystic kidney disease (PKD) spectrum.

Overall, the detection rate of renal cysts in patients with *HNF1B* mutations is comparable across the published studies performed by pediatric nephrologists (84% in [11], 94% in [13]). In addition, both isolated bilateral hyperechogenic kidneys and cystic dysplasia in the antenatal period can be highly indicative of *HNF1B* nephropathy [13, 14], and a postnatal diagnostic clarification is strongly advised for these newborns including a renal ultrasound in their parents.

Renal function

Among a subset of *HNF1B* patients, CRF and ESRD seem to develop when the patients are very young. Five patients rapidly developed ESRD with a GFR below $30 \text{ ml/min/1.73m}^2$ already at an early age. Extrarenal symptoms did not differ from the rest of the cohort but all were affected by severe bilateral dysplasia. ESRD is a sequela of severe dysplasia of both kidneys, independent of the underlying gene mutation. Presumably, additional genetic factors or modifiers, environmental factors, or epigenetic influences aggravate the disease

in this subset of patients. Similar observations have been made in the subset of young children with VEO-ADPKD [36], for whom additional genetic variants were identified in *PKHD1* or *HNF1B* and were presumed to act as disease modifiers. VEO-*HNF1B* nephropathy requires special attention and medical care, including early renal replacement therapy.

Non-VEO-*HNF1B* nephropathy has a more favorable course, with only a slow decline of renal function over time during childhood; normal renal function is preserved for many children. In children with cyst progression, the annual decline in GFR seems to be pronounced. In previous studies, a normal GFR ($70 \text{ ml/min/1.73m}^2$ or higher) was documented in 56% of pediatric study patients in [11] and in 39% of pediatric study patients in [13]. During adulthood, loss of renal function seems to accelerate, as suggested by the results of Faguer et al. in a series of 27 adult *HNF1B* patients with a median annual decrease in GFR of $-2.45 \text{ ml/min/1.73m}^2$ [37]. Continuous follow-up of the pediatric registry with transition into adulthood will be important for defining this acceleration of decline in renal function as patients' age increases. Possible causes might be related to arterial hypertension, DM, proteinuria, or dietary salt intake.

Extrarenal manifestations

Hypomagnesemia was diagnosed in 24% of our study patients but higher rates have been reported in cohorts composed mostly of older patients. Renal magnesium wasting in *HNF1B* disease was first described in [9] in 44% of 21 patients. Faguer et al. reported hypomagnesemia ($\text{Mg} < 0.75 \text{ mmol/l}$) in 63% of patients with a median age of 35 years at last follow-up [37]. In a case series of three adult male patients, pronounced hypomagnesemia was the first clinical manifestation of ADTKD-*HNF1B* [38]. Besides significant differences in defining hypomagnesemia, the development of this condition seems to be strongly age-related.

Hyperuricemia was documented in 37% of our study patients, with an early onset at a median patient age of 1 year. Only 20% of patients in the study by Bingham et al. [39] exhibited elevated uric acid levels. Because uric acid concentrations are not routinely measured at many pediatric centers, hyperuricemia may be underdiagnosed. Among patients with kidney dysplasia, hyperuricemia disproportionate to renal function highly suggests *HNF1B* nephropathy as underlying cause. However, an important differential diagnosis is ADTKD caused by variants in uromodulin (ADTKD-*UMOD*), presenting as familial juvenile hyperuricemic nephropathy and MCKD [40, 41]. The cause of hyperuricemia in both ADTKD-*UMOD* and ADTKD-*HNF1B* is not well understood, but hyperuricemia seems to be a consequence of tubulointerstitial dysfunction. Novel experimental studies have linked *HNF1B* to mitochondrial energy metabolism in renal tubular cells [42] providing a possible link to

transcellular substrate movements. More experimental work will be necessary for better defining the role of *HNFI1B* in uric acid transport and metabolism.

Hyperglycemia, elevated HbA1c levels, or both were found in only 8% of our patients. Decramer et al. [13] found DM in 17% of patients; Bingham et al. [39] in 58% (mean age at diagnosis 25 years); Faguer et al. [37] in 48% (median age 35 years); and Edghill et al. [43] in 48%. These results indicate that impaired glucose tolerance and DM are rarely observed in childhood but, even more so than hypomagnesemia, develop later in the clinical course of *HNFI1B* disease. However, under certain circumstances, e.g., after renal transplantation with concomitant high doses of steroids, tacrolimus, or both, DM may be unmasked in *HNFI1B*-positive patients [44], requiring specific treatment and often a change in the immunosuppressive regimen. New-onset diabetes after transplant (NODAT) is a serious complication compromising renal graft function [45]. Therefore, screening for *HNFI1B* mutations should be considered pre-transplant for patients with ESRD caused by (cystic) kidney dysplasia. In a subgroup of patients, *HNFI1B* disease first manifests as a disturbance of glucose metabolism [46]. A recent Norwegian study estimated that the overall prevalence of monogenic diabetes gene mutations (including *HNFI1A*, *HNFI4A*, *HNFI1B*, *GCK*, and *INS*) in children with autoantibody-negative DM is very rare with 6.5% [47]. A study using high-throughput genetic analysis of 4016 patients with type 2 DM (34% with age at diagnosis of <40 years) identified only one *HNFI1B* mutation (age at diagnosis 14 years), whereas mutations in *HNFI1A* and *GCK* occurred much more frequently [48]. *HNFI1B* seems to play a minor role in children (and adults) with isolated autoantibody-negative DM.

Elevated liver enzyme activity was detected in 21% of our patients, in 13% in [39], and in 40% in [37]; thus, there is a high degree of variability among the separate studies. Results of liver ultrasound seem to be normal in most cases reported so far; however, a longitudinal follow-up of our pediatric patients into adulthood will be of interest in elucidating the long-term effects of liver dysfunction in *HNFI1B* disease.

Genital tract anomalies resulting from Müllerian duct aplasia and failure of fusion of the Müllerian ducts have repeatedly been described in patients with *HNFI1B* mutations [49, 50]. In our cohort, only one patient was found to have hypoplastic testicles and no other urogenital abnormalities were detected. Bingham et al. [39] described uterine malformations in 14% of female patients and genital tract malformations in 5% of male patients. Edghill et al. [43] found genital tract anomalies in 9% of patients. Oram et al. identified mutations in *HNFI1B* in 18% (9/50) of women with combined uterine and renal abnormalities but in none (0/58) with isolated malformations of the uterus [51]. Overall, genital tract malformations are an inconsistent finding. However, when

they are combined with renal abnormalities, *HNFI1B* mutation analysis seems advised.

In summary, this report presents the results of a longitudinal dataset from one of the largest pediatric cohorts of patients with *HNFI1B* nephropathy. With few exceptions, *HNFI1B* nephropathy among children is a rather non-progressive disorder with respect to cyst development and a slowly progressive disease with respect to kidney damage. In contrast, VEO-*HNFI1B* nephropathy is associated with high morbidity rates and early ESRD. Hyperuricemia is a frequent finding in very young patients, whereas the prevalence of hypomagnesemia, elevated liver enzyme activity, and hyperglycemia is higher among teenagers. A close genotype-phenotype correlation is lacking; however, we describe a significant parent-of-origin effect in *HNFI1B* disease, with an 80% preponderance of maternal inheritance. Future studies employing the combined efforts of international registries are necessary for identifying the underlying mechanisms.

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Compliance with ethical standards

The study was approved by the ethics committees of the University Duisburg-Essen and all collaborating institutions, according to the Declaration of Helsinki. Written informed consent was obtained.

Conflict of interest The authors declare that they have no conflict of interest.

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